Multi-Stage Modeling of the Kinetics of Activation of CaMKII

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Ca^{2+}/calmodulin-dependent protein kinase 2 (CaMKII) plays an important role in induction of long-term potentiation and formation of memory. It is abundant in dendritic spines, and is activated when Ca^{2+} flows into the postsynaptic cytosol through open NMDA-type glutamate receptors. Its function is fine-tuned through interaction with other proteins as well as through subunit interactions and regulatory autophosphorylation. We have undertaken a multi-stage project to study the critical kinetics of activation of CaMKII in the spine by combining modeling and experimental studies. We are using computational modeling and simulations on various platforms, coupled with biochemical experiments in vitro, and eventually in vivo, to understand CaMKII regulation. The project includes the following steps:

1. Determining the parameters governing activation of a monomeric subunit.

The CaMKII holoenzyme is a large dodecamer of similar, homologous subunits held together by interactions between the association domains located at the carboxyl end of each subunit. Individual, monomeric subunits can be expressed recombinantly by removing the association domain. Computer simulations of activation of monomeric CaMKII by Ca^{2+}/calmodulin at both saturating and non-saturating concentrations in a test tube have helped to identify the binding parameters that are most crucial for modeling of regulation of CaMKII and thus have indicated the most useful biochemical assays to measure those parameters (Pepke et al., 2010). We are using these measurements to fine-tune our model of activation of individual catalytic subunits.

2. Building a model of the holoenzyme.

Because a CaMKII holoenzyme contains 12 similar subunits, each of which can exist in several states, the holoenzyme can have a large number of state combinations. Thus, modeling the entire holoenzyme requires a computational framework that avoids the ensuing combinatorial complexity. The stochastic simulator MCell provides an elegant, rule-based way of modeling state changes in the CaMKII holoenzyme.

3. Modeling cooperativity that arises from the dodecameric structure of CaMKII.

Autophosphorylation at threonine-286, which activates CaMKII subunits, is an inter-subunit event. Thus, it is greatly facilitated by the close proximity of subunits in the holoenzyme. In addition, the subunits within the holoenzyme are arranged as dimers which appears to result in cooperativity in the binding of Ca^{2+}/CaM to individual subunits of the dimer (Chao et al., 2010). An accurate model of activation of subunits in the holoenzyme and their autophosphorylation will allow us to explore the effects of cooperativity on CaMKII activation on various time scales.

4. Modeling CaMKII within the context of a postsynaptic spine.

CaMKII interacts with a variety of other proteins, both in the postsynaptic density (PSD), close to major sources of Ca^{2+} influx, and in other parts of the spine. In the fourth stage of this project we plan to implement kinetic models of activation of CaMKII in the context of an MCell model of Ca^{2+} influx into a spine upon activation of NMDA-type glutamate receptors (Keller et al., 2008; Keller et al., 2011, submitted). We will explore the effects of different localization and numbers of CaMKII holoenzymes in the spine on CaMKII activation.

References:

Pepke, S., Kinzer-Ursem, T., Mihalas, S., and Kennedy, M.B. (2010). A dynamic model of interactions of Ca^{2+}, calmodulin, and catalytic subunits of Ca^{2+}/calmodulin-dependent protein kinase II. PLoS Comput Biol 6, e1000675.

Chao, L.H., Pellicena, P., Deindl, S., Barclay, L.A., Schulman, H., and Kuriyan, J. (2010). Intersubunit capture of regulatory segments is a component of cooperative CaMKII activation. Nat Struct Mol Biol *17*, 264-272.

Keller, D.X., Franks, K.M., Bartol, T.M., Jr., and Sejnowski, T.J. (2008). Calmodulin activation by calcium transients in the postsynaptic density of dendritic spines. PLoS ONE *3*, e2045.

Keller, D.X., Bartol, T.M., Kinney, J.P, Kennedy, M.B., Bajaj, C., Harris, K.M., and Sejnowski, T.J. Regulation of synaptic calcium transients in reconstructed dendritic spines of hippocampal CA1 pyramidal neurons, submitted.